

What is claimed is:

1. A method for selecting a panel of biomarkers useful for determining the stage of sepsis in an animal species comprising:

(a) providing a plurality of biological samples taken at a selected timepoint from at least two groups of animals, wherein the first group of animals comprises survived immunocompromised individuals infected by a sepsis-causing pathogen and the second group of animals comprises doomed immunocompromised individuals infected by a sepsis-causing pathogen;

(b) measuring the amount of each of a plurality of analytes in the biological samples from each group and generating a dataset for each group; and

(c) performing a statistical analysis on the data comprising:

(i) conducting a univariate statistical test on the dataset for each analyte, to compare the dataset for biological samples from the first group to the dataset for biological samples from the second group of animals; and

(ii) selecting as biomarkers analytes according to their significance level as determined by the univariate statistical test.

2. The method of claim 1 wherein the univariate statistical test is a T-test.

3. The method of claim 1 further comprising transforming the data for each group to log scale.

4. The method of claim 1, wherein the p value of each of the selected analytes is less than a significance level of 0.05.

5. The method of claim 1 further comprising:

deriving a discrimination function for the selected biomarkers, wherein said deriving comprises performing a principle component analysis and a linear discriminant analysis; and using the discrimination function to generate a score for each animal.

6. The method of claim 5, wherein the analytes comprise MCP-1/JE, IL-6, MCP-3, IL-3, MIP-1 β , and KC-GRO.

7. The method of claim 6 wherein the discrimination function is $19(\text{MCP-1-JE}) + 27(\text{IL-6}) + 18(\text{MCP-3}) + 21(\text{IL-3}) + 18(\text{MIP-1}\beta) + 25(\text{KC-GRO})$.

8. The method of claim 1, wherein the analytes comprise Apolipoprotein A1, β 2 Microglobulin, C Reactive Protein, D-dimer, EGF, Endothelin-1, Eotaxin, Factor VII, FGF-9, FGF-Basic, Fibrinogen, GCP-2, LIX, GM-CSF, Growth Hormone, GST, Haptoglobin, IFN-

α , IgA, IL-10, IL-11, IL-12p70, IL-17, IL-18, IL-1 α , IL-1 β , IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, Insulin, IP-10, KC-GRO, Leptin, LIF, Lymphotoctin, MCP-1-JE, MCP-3, MCP-5, M-CSF, MDC, MIP-1 α , MIP-1 β , MIP-1 α , MIP-2, MIP-3 β , Myoglobin, OSM, RANTES, SCF, SGOT, TIMP-1, Tissue Factor, TNF- α , TPO, VCAM-1, VEGF, and VWF.

9. The method of claim 1, wherein the animals are mice.

10. The method of claim 8, wherein the timepoint is selected from the group consisting of 4 hours post infection, 10 hours post infection, 22 hours post infection, 24 hours post infection, 48 hours post infection, 72 hours post infection, and 96 hours post infection.

11. The method of claim 1, wherein the species is human.

12. The method of claim 1, wherein the biomarker panel consists of fifteen or fewer biomarkers.

13. The method of claim 1, wherein the biomarker panel consists of ten or fewer biomarkers.

14. The method of claim 1, wherein the biomarker panel consists of five or fewer biomarkers.

15. The method of claim 1, further comprising using data-visualization software to evaluate the ability of the panel biomarkers to predict disease outcome for a subject diagnosed with sepsis.

16. The method of claim 1, wherein the biological samples are serum samples.

17. A method for providing a survival prognosis for an animal diagnosed with sepsis, comprising:

(a) providing a biological sample from an animal suspected of being infected by a sepsis-causing pathogen;

(b) providing a panel of biomarkers useful for determining the stage of sepsis syndrome in the animal species, said panel selected according to the method defined in claim 5;

(c) measuring in the biological sample the amount of each of the biomarkers;

(d) generating a score for the biological sample using the discrimination function;

and

(e) comparing the score with at least one score determined using a biological sample from a survived immunocompromised animal and at least one score determined using a biological sample from a doomed immunocompromised animal.

18. The method of claim 17, further comprising confirming that the animal is infected by a sepsis-causing pathogen.
 19. The method of claim 17 wherein the animal species is a mammal.
 20. The method of claim 17 where the animal is a mouse.
 21. The method of claim 17 where the animal is a human.
 22. A method for determining the stage of sepsis in an animal comprising:
 - (a) providing a biological sample from an animal suspected of being infected by a sepsis-causing pathogen;
 - (b) providing a panel of biomarkers useful for determining the stage of sepsis syndrome in the animal species, said panel selected according to the method defined in claim 5;
 - (c) measuring in the biological sample the amount of each of the biomarkers;
 - (d) generating a score for the biological sample using a discrimination function determined for the stage of sepsis syndrome; and
 - (e) comparing the score for the biological sample with at least one reference score determined using a biological sample from at least one animal in said stage of sepsis syndrome.
 23. The method of claim 22 further comprising confirming that the animal is infected by a sepsis-causing pathogen.
 24. The method of claim 22 where the animal is a mammal.
 25. The method of claim 22 where the animal is a mouse.
 26. The method of claim 22 where the animal is a human.
 27. A method of evaluating a test compound for treating sepsis syndrome, comprising:
 - (a) developing experimental animals modeling sepsis syndrome, comprising infecting experimental immunocompromised animals and control immunocompromised animals of the same species with a pathogen species a pathogen species capable of causing sepsis in the animal species, wherein the survival rate of immunocompromised infected animals in the model system is 10-90%;
 - (b) administering a test compound to the experimental animals;
 - (c) obtaining biological samples from the experimental and control animals at a selected timepoint following infection;
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(d) measuring the amounts of a plurality of analytes in the biological samples;
and

(e) determining the scores for the experimental and control animals using a discrimination function for the animal species;

whereby if the test compound is determined to be effective in causing a statistically significant change in the score for the biological sample compared to the score for the control animals, the test compound is a candidate drug for treating sepsis syndrome.

28. The method of claim 27 wherein said test compound is a modulator of vascular endothelial growth factor, monocyte chemoattractant protein 1, or peroxisome proliferator-activated receptor gamma.

29. The method of claim 27, wherein said survival rate of immunocompromised infected animals in the model system is 30-70%.

30. The method of claim 27 wherein the test compound is a toll-like receptor (TLR) inhibitor.

31. The method of claim 27, further comprising administering an antibiotic to the animals.

32. A method of determining a reference score for a group of immunocompromised infected animals in a model system comprising:

(a) providing a model system of sepsis syndrome, said model system comprising immunocompromised survived animals and immunocompromised doomed animals from an animal species and a sepsis-causing pathogen species;

(b) infecting the animals in the model system;

(c) obtaining biological samples from the animals at a selected time after infecting;

(d) measuring the level of a panel of biomarkers selected using the method of claim 5 in each biological sample; and

(e) determining a first reference score for immunocompromised survived animals using a discrimination function, and determining a second reference score for immunocompromised doomed animals using a discrimination function.

33. A method of determining a reference score for a group of sepsis patients comprising:

- (a) providing a group of patients having sepsis;
 - (b) obtaining biological samples from said patients;
 - (c) measuring the level of a panel of biomarkers selected using the method of claims 5 in each biological sample; and
 - (d) determining a first reference score for actual doomed patients with sepsis using a discrimination function, and determining a second reference score for actual survived patients using a discrimination function.
34. A method as defined in claim 33, wherein the biomarker panel comprises an MCP-1 analyte.
35. A method as defined in claim 34, wherein the biomarker panel further comprises a VEGF analyte.
36. A model system for septic syndrome comprising:
- (a) at least one immunocompromised animal infected with a sepsis-causing pathogen; and
 - (b) at least one immunocompromised animal not infected with a sepsis-causing pathogen.
37. A method of using the model system of claim 36 to test the effectiveness of a compound active against a sepsis target, comprising:
- (a) providing a test compound to said at least one infected animal and to said at least one not infected animal;
 - (b) determining the survival rate for each said treated animal; and
 - (c) determining the level of at least one serum analyte in each said treated animal,
- whereby change in the survival rates and the at least one analyte level reflects the effectiveness of the compound as a treatment for septic syndrome.
38. The method of claim 37, wherein said animals are each a mouse.
39. The method of claim 37, wherein the test compound is an anti-vascular endothelial growth factor (VEGF) antibody or an anti-MCP-1 antibody.
40. The method of claim 37, further comprising administering an antibiotic to the animals.
41. A method for identifying biomarkers involved in the systemic inflammatory response to infection comprising:

(a) providing a plurality of biological samples taken at a selected timepoint from at least two groups of animals wherein the first group comprises survived immunocompromised individuals infected by a sepsis-causing pathogen and the second group comprises doomed immunocompromised individuals infected by a sepsis-causing pathogen;

(b) measuring the amount of each of a plurality of analytes in the biological samples from each group and generating a dataset for each group; and

(c) performing a statistical analysis on the data comprising:

(i) conducting a univariate statistical test on the dataset, for each analyte, to compare the dataset for biological samples from the first group to the dataset for biological samples from the second group of animals; and

(ii) selecting analytes according to their significance level as determined by the univariate statistical test.

42. A method for selecting a panel of biomarkers useful for determining the stage of sepsis in an animal species comprising:

(a) providing a plurality of biological samples taken at a selected timepoint from at least two groups of animals wherein the first group comprises survived immunocompromised individuals infected by a sepsis-causing pathogen and the second group comprises doomed immunocompromised individuals infected by a sepsis-causing pathogen;

(b) measuring the amount of each of a plurality of analytes in the biological samples from each group and generating a dataset for each group; and

(c) selecting analytes according to their ability to discriminate between the groups.

43. A method of treating sepsis, comprising administering to a subject in need of such treatment a therapeutically effective amount of a compound modulating MCP-1 activity.

44. A method as defined in claim 43, wherein said compound is an anti-MCP-1 antibody.